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For the Patent- and Registration Office

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NOVEL COMPOUNDS

The present invention relates to a sulphonamide compound, processes and intermediates used in their preparation, pharmaceutical compositions containing them and their use in therapy.

Chemokines play an important role in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small-secreted molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved four cysteine motif. At the present time, the chemokine superfamily comprises three groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C), Cys-Cys (C-C) and Cys-X_3-Cys (C-X_3-C) families. The C-X-C and C-C families have sequence similarity and are distinguished from one another on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues. The C-X_3-C family is distinguished from the other two families on the basis of having a triple amino acid insertion between the NH-proximal pair of cysteine residues.

The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

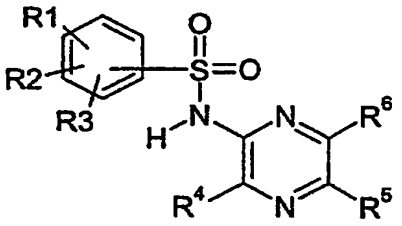
The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils. Examples include human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1α and 1β (MIP-1α and MIP-1β), Thymus and Activation Regulated Chemokine (TARC, CCL17) and Macrophage Derived Chemokine (MDC, CCL22).

The C-X_3-C chemokine (also known as fractalkine) is a potent chemoattractant and activator of microglia in the central nervous system (CNS) as well as of monocytes, T cells, NK cells and mast cells.

Studies have demonstrated that the actions of chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11

(for the C-C family); CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5 (for the C-X-C family) and CX_3CR1 for the C-X_3-C family. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

The present invention therefore provides a compound of formula (I) and pharmaceutically acceptable salts or solvates thereof for use in therapy:



(I)

in which

R^1, R^2 and R^3 are independently hydrogen, halogen, cyano, C_{1-6} alkenyl or C_{1-6} alkyl;

R^4 is OR^9;

R^5 and R^6 are independently hydrogen, halogen, C_{1-6} alkoxy, C_{1-6} alkylthio, R^9, OR^9, NR^9R^{10} or SR^9;

R^9 and R^{10} are independently hydrogen, C_{1-6} alkyl, optionally substituted aryl, C_{1-6} alkyl-aryl or C_{1-6} alkyl-R^{11}; and

R^{11} is a 5- to 7-membered heteraromatic ring containing 1 to 3 heteroatoms selected from nitrogen, oxygen and sulphur.

The term aryl includes phenyl and naphthyl. Optional substituents for aryl groups include C_{1-6} alkyl, C_{1-6} alkoxy, halogen, CN, nitro, CO_2H, CO_2C_{1-6} alkyl etc. The term alkyl, whether alone or as part of another group, includes straight chain and branched chain alkyl groups. Examples of 5- to 7-membered heteraromatic ring containing 1 to 3 heteroatoms include thienyl, furyl, imidazolyl, pyridyl and pyrimidyl

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

R^1, R^2 and R^3 are independently hydrogen, halogen, cyano, C_{1-6} alkenyl or C_{1-6} alkyl, preferred halogen groups being chloro. Preferably one of R^1, R^2 and R^3 is methyl, ethenyl, cyano, chloro, fluoro, iodo or two are chloro or all three are fluoro. More preferably the phenyl group is ?/ any preferred??/.

Preferred groups for R^4 include C_{1-6} alkoxy such as methoxy and ethoxy, or C_{1-6} alkyl. More preferably R^4 is methoxy or methyl.

Preferably R^5 and R^6 are both hydrogen.

Preferred compounds of formula (I) include:

2,3-Dichloro-N-(3-methoxy-5-methyl-2-pyrazinyl)-benzenesulphonamide

N-(6-Chloro-3-methoxy-2-pyrazinyl)-2,3,4-tifluorobenzenesulphonamide

3-Chloro-N-(6-Chloro-3-methoxy-2-pyrazinyl)-2-methylbenzenesulphonamide

2,3-Dichloro-N-(6-Chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide

2,3-Dichloro-N-(5-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide

N-(5-Bromo-3-methoxy-2-pyrazinyl)-2,5-dichlorobenzenesulphonamide

N-(5-Bromo-3-methoxy-2-pyrazinyl)-3,5-dichlorobenzenesulphonamide

N-(5-Bromo-3-methoxy-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide

N-(5-Bromo-3-methoxy-2-pyrazinyl)-2,4-dichlorobenzenesulphonamide

N-(5-Bromo-3-methoxy-2-pyrazinyl)-3,4-dichlorobenzenesulphonamide

N-(5-Bromo-3-methoxy-2-pyrazinyl)-4-chlorobenzenesulphonamide

N-(5-Bromo-3-methoxy-2-pyrazinyl)-3-chlorobenzenesulphonamide

pyrazinamine and 3-chlorobenzenesulphonyl chloride.

N-(5-Bromo-3-methoxy-2-pyrazinyl)-2-ethenylbenzenesulphonamide

N-(5-Bromo-3-methoxy-2-pyrazinyl)-2-fluorobenzenesulphonamide

N-(3-Methoxy-5-methyl-2-pyrazinyl)benzenesulphonamide

N-(3-Methoxy-5-methyl-2-pyrazinyl)-2-iodobenzenesulphonamide

N-(3-Methoxy-5-methyl-2-pyrazinyl)-3-fluorobenzenesulphonamide

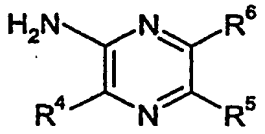
2-[[(3-Methoxy-5-methyl-2-pyrazinyl)amino]sulphonyl]benzonitrile

N-(5-Bromo-3-methoxy-2-pyrazinyl)benzenesulphonamide

N-(5-Bromo-3-methoxy-2-pyrazinyl)2-iodobenzenesulphonamide

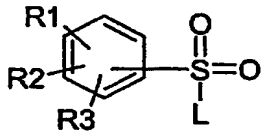
and pharmaceutically acceptable salts and solvates thereof.

According to the invention there is also provided a process for the preparation of compound (I) which comprises reaction of a compound of formula (II):



(II)

where R^4, R^5 and R^6 are as defined in formula (I) or are protected derivatives thereof with a compound of formula (III):



(III)

where R^1, R^2 and R^3 are as defined in formula (I) or are protected derivatives thereof and L is a leaving group,
and optionally thereafter
removing any protecting groups,
forming a pharmaceutically acceptable salt.

Preferred leaving groups L include chloro. Preferably the reaction between compounds (II) and (III) is carried out by treating compound (II) with a base such as sodium hydride in a suitable solvent such as DME.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the starting reagents or intermediate compound may need to be protected by protecting groups. Thus,

the preparation of the compound of formula (I) may involve, at an appropriate stage, the removal of one or more protecting groups. The protection and deprotection of functional groups is fully described in 'Protective Groups in Organic Chemistry', edited by J. W. F. McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis', 2nd edition, T. W. Greene & P. G. M. Wuts, Wiley–Interscience (1991).

Intermediate compounds of formula (II) and (III) can be prepared using standard chemistry or are available commercially.

Certain compounds of formula (I) are believed to be novel and form a further aspect of the invention.

The compounds of formula (I) above may be converted to a pharmaceutically acceptable salt or solvate thereof, preferably a basic addition salt such as sodium, potassium, calcium, aluminium, lithium, magnesium, zinc, benzathine, chloroprocaine, choline, diethanolamine, ethanolamine, ethyldiamine, meglumine, tromethamine or procaine, or an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate.

The compounds of formula (I) has activity as pharmaceuticals, in particular as modulators of chemokine receptor (especially CCR4) activity, and may be used in the treatment (therapeutic or prophylactic) of conditions/diseases in human and non-human animals which are exacerbated or caused by excessive or unregulated production of chemokines. Examples of such conditions/diseases include:

(1) **(the respiratory tract)** obstructive airways diseases including chronic obstructive pulmonary disease (COPD); asthma, such as bronchial, allergic, intrinsic, extrinsic and dust asthma, particularly chronic or inveterate asthma (e.g. late asthma and airways hyper-responsiveness); bronchitis; acute, allergic, atrophic rhinitis and chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca and rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous and pseudomembranous rhinitis and scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) and vasomotor rhinitis; sarcoidosis, farmer's lung and related diseases, fibroid lung and idiopathic interstitial pneumonia;

(2) **(bone and joints)** rheumatoid arthritis, seronegative spondyloarthropathies (including ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome and systemic sclerosis;

(3) **(skin)** psoriasis, atopical dermatitis, contact dermatitis and other eczmatous dermitides, seborrhoetic dermatitis, Lichen planus, Pemphigus, bullous Pemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides, erythemas, cutaneous eosinophilias, uveitis, Alopecia areata and vernal conjunctivitis, lupus;

(4) **(gastrointestinal tract)** Coeliac disease, proctitis, eosinopilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, food-related allergies which have effects remote from the gut, e.g., migraine, rhinitis and eczema;

(5) **(central and peripheral nervous system)** Neurodegenerative diseases and dementia disorders, e.g. Alzheimer's disease, amyotrophic lateral sclerosis and other motor neuron diseases, Creutzfeldt-Jacob's disease and other prion diseases, HIV encephalopathy (AIDS dementia complex), Huntington's disease, frontotemporal dementia, Lewy body dementia and vascular dementia; polyneuropathies, e.g. Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, multifocal motor neuropathy, plexopathies; CNS demyelination, e.g. multiple sclerosis, acute disseminated/haemorrhagic encephalomyelitis, and subacute sclerosing panencephalitis; neuromuscular disorders, e.g. myasthenia gravis and Lambert-Eaton syndrome; spinal diorders, e.g. tropical spastic paraparesis, and stiff-man syndrome: paraneoplastic syndromes, e.g. cerebellar degeneration and encephalomyelitis; CNS trauma; migraine; and stroke.

(6) **(other tissues and systemic disease)** atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus erythematosus, systemic lupus, erythematosus, Hashimoto's thyroiditis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, lepromatous leprosy, and idiopathic thrombocytopenia pupura; post-operative adhesions, and sepsis.

(7) (allograft rejection) acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin and cornea; and chronic graft versus host disease;

(8) Cancers, especially non-small cell lung cancer (NSCLC), malignant melanoma, prostate cancer and squamous sarcoma, Hodgkins Lymphoma, Acute Lymphoblastic Leukemia, and tumour metastasis;

(9) All diseases that result from a general inbalance of the immune system and resulting in increased atopic inflammatory reactions.

(10) Cystic fibrosis, re-perfusion injury in the heart, brain, peripheral limbs and other organs.

(11) Burn wounds & chronic skin ulcers

(12) Reproductive Diseases (e.g. Disorders of ovulation, menstruation and implantation, Pre-term labour, Endometriosis)

Thus, the present invention provides a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

Preferably the compound of the invention are used to treat diseases in which the chemokine receptor belongs to the CC chemokine receptor subfamily, more preferably the target chemokine receptor is the CCR4 receptor.

Particular conditions which can be treated with the compound of the invention are asthma, rhinitis and inflammatory skin disorders, diseases in which there are raised TARC, MDC or CCR4 levels. It is preferred that the compound of the invention is used to treat asthma and rhinitis, especially asthma.

In a further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In a still further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the

manufacture of a medicament for the treatment of human diseases or conditions in which modulation of chemokine receptor activity, particularly CCR4 activity, is beneficial.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

The invention still further provides a method of treating a chemokine mediated disease wherein the chemokine binds to a chemokine (especially CCR4) receptor, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

The invention also provides a method of treating a respiratory disease, such as athma and rhinitis, especially asthma, in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

The compound of formula (I) and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

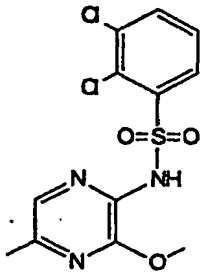
The present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally. Preferably the compound of the invention is administered orally.

Example 1

2,3-Dichloro-N-(3-methoxy-5-methyl-2-pyrazinyl)-benzenesulphonamide



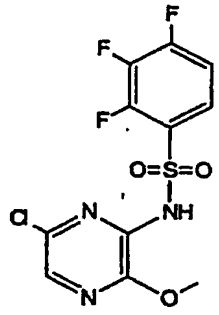
Sodium hydride (0.1g of 60%) was added to 3-methoxy-5-methyl-2-pyrazinamine (0.07g) in 1,2-dimethoxyethane (3mL) under nitrogen at room temperature. After 1 hour at 50°, 2,3-dichlorobenzenesuphonyl chloride (0.15g) was added. After stirring for 30 minutes, 5% aqueous citric acid was added and the product extracted with ethyl acetate (X3). The combined extracts were washed with saturated brine, dried ($MgSO_4$) and the solvent was evaporated. Chromatography on silica eluting with dichloromethane/methanol mixtures gave the title compound as a white solid (0.08g).

m/e 346/8/350 ($M-1^+$, 100%), HPLC 98.8%

^{1}H NMR (D6-DMSO) δ 11.27 (1H, s), 8.06 (1H, d), 7.93 (1H, d), 7.60-7.55 (1H, br s), 7.58 (1H, t), 3.87 (3H, s) and 2.28 (3H, s).

Example 2

N-(6-Chloro-3-methoxy-2-pyrazinyl)-2,3,4-tifluorobenzenesulphonamide



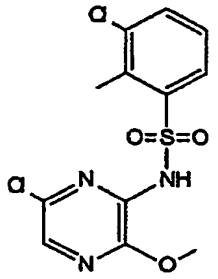
Prepared by the method of Example 1 using 6-chloro-3-methoxy-2-pyrazinamine and 2,3,4-trifluorobenzenesulphonyl chloride.

m/e 352/4 ($M-1^+$, 100%), HPLC 98.8%

^{1}H NMR (D6-DMSO) δ 7.93-7.80 (1H, m), 7.89 (1H, s), 7.60-7.50 (1H, m) and 3.91 (3H, s).

Example 3

3-Chloro-N-(6-Chloro-3-methoxy-2-pyrazinyl)-2-methylbenzenesulphonamide



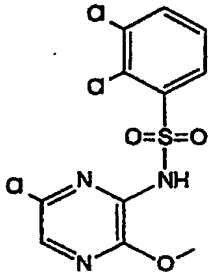
Prepared by the method of Example 1 using 6-chloro-3-methoxy-2-pyrazinamine and 3-chloro-2-methylbenzenesulphonyl chloride.

m/e 346/8/50 (M-1$^+$, 100%), HPLC 100%

^{1}H NMR (D6-DMSO) δ 8.05 (1H, d), 7.85 (1H, s), 7.75 (1H, d), 7.47 (1H, t), 3.92 (3H, s) and 2.66 (3H, s).

Example 4

2,3-Dichloro-N-(6-Chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide



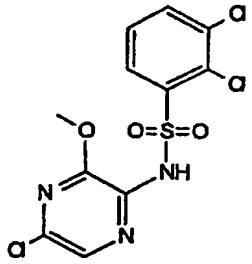
Prepared by the method of Example 1 using 6-chloro-3-methoxy-2-pyrazinamine and 2,3-dichlorobenzenesulphonyl chloride.

m/e 366/8/370/2 (M-1$^+$, 100%), HPLC 100%

^{1}H NMR (D6-DMSO) δ 8.14 (1H, d), 7.96 (1H, d), 7.89 (1H, s), 7.62 (1H, t) and 3.91 (3H, s).

Example 5

2,3-Dichloro-N-(5-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide



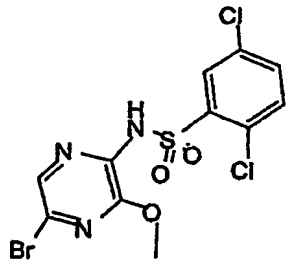
Prepared by the method of Example 1 using 5-chloro-3-methoxy-2-pyrazinamine and 2,3-dichlorobenzenesulphonyl chloride.

m/e 366/8/370/2 ($M-1^+$, 100%), HPLC 99.6%

^{1}H NMR (D6-DMSO) δ 8.15 (1H, d), 7.93 (1H, d), 7.79 (1H, s), 7.58 (1H, t) and 3.93 (3H, s).

Example 6

N-(5-Bromo-3-methoxy-2-pyrazinyl)-2,5-dichlorobenzenesulphonamide



Prepared by the method of Example 1 using 5-bromo-3-methoxy-2-pyrazinamine and 2,5-dichlorobenzenesulphonyl chloride.

m/e 410/2/4/6 ($M-1^+$, 100%), HPLC 98.0%

^{1}H NMR (D6-DMSO) δ 8.04 (1H, d), 7.86 (1H, s), 7.73 (1H, dd), 7.66 (1H, dd) and 3.91 (3H, s).

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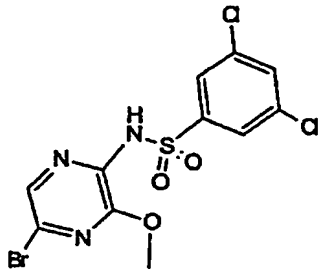
Example 7

N-(5-Bromo-3-methoxy-2-pyrazinyl)-3,5-dichlorobenzenesulphonamide



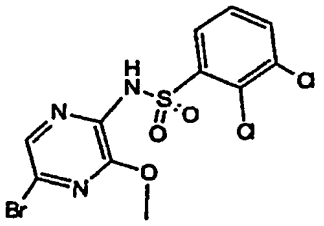
Prepared by the method of Example 1 using 5-bromo-3-methoxy-2-pyrazinamine and 3,5-dichlorobenzenesulphonyl chloride.

m/e 410/2/4/6 ($M\text{-}1^+$, 100%), HPLC 96.1%

^{1}H NMR (D6-DMSO) δ 7.96-7.91 (4H, m) and 3.93 (3H, s).

Example 8

N-(5-Bromo-3-methoxy-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide



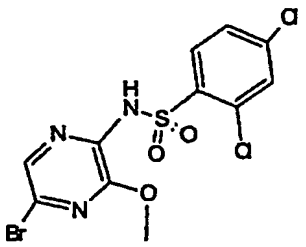
Prepared by the method of Example 1 using 5-bromo-3-methoxy-2-pyrazinamine and 2,3-dichlorobenzenesulphonyl chloride.

m/e 410/2/4/6 ($M\text{-}1^+$, 100%), HPLC 97.3%

^{1}H NMR (D6-DMSO) δ 8.06 (1H, dd), 7.93 (1H, dd), 7.82 (1H, s), 7.57 (1H, t) and 3.92 (3H, s).

Example 9

N-(5-Bromo-3-methoxy-2-pyrazinyl)-2,4-dichlorobenzenesulphonamide



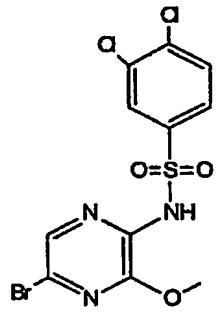
Prepared by the method of Example 1 using 5-bromo-3-methoxy-2-pyrazinamine and 2,4-dichlorobenzenesulphonyl chloride.

m/e 410/2/4/6 (M-1$^+$, 100%), HPLC 99.9%

^{1}H NMR (D6-DMSO) δ 8.07 (1H, d), 7.85 (2H, d), 7.64 (1H, dd) and 3.92 (3H, s).

Example 10

N-(5-Bromo-3-methoxy-2-pyrazinyl)-3,4-dichlorobenzenesulphonamide



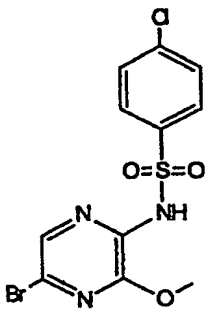
Prepared by the method of Example 1 using 5-bromo-3-methoxy-2-pyrazinamine and 3,4-dichlorobenzenesulphonyl chloride.

m/e 410/2/4/6 (M-1$^+$, 100%), HPLC 98.8%

^{1}H NMR (D6-DMSO) δ 8.14 (1H, s), 8.00-7.85 (3H, m) and 3.94 (3H, s).

Example 11

N-(5-Bromo-3-methoxy-2-pyrazinyl)-4-chlorobenzenesulphonamide



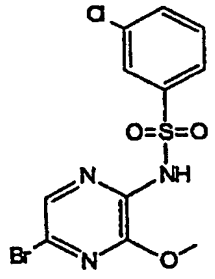
Prepared by the method of Example 1 using 5-bromo-3-methoxy-2-pyrazinamine and 4-chlorobenzenesulphonyl chloride.

m/e 376/8/380 ($M-1^+$, 100%), HPLC 98.8%

^{1}H NMR (D6-DMSO) δ 11.3 (1H, br s), 7.97 (2H, d), 7.91 (1H, s), 7.66 (2H, d) and 3.93 (3H, s).

Example 12

N-(5-Bromo-3-methoxy-2-pyrazinyl)-3-chlorobenzenesulphonamide



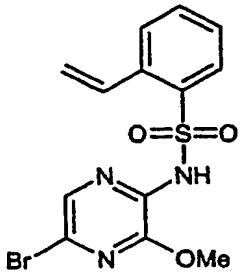
Prepared by the method of Example 1 using 5-bromo-3-methoxy-2-pyrazinamine and 3-chlorobenzenesulphonyl chloride.

m/e 376/8/380 ($M-1^+$, 100%), HPLC 97.8%

^{1}H NMR (D6-DMSO) δ 8.00-7.90 (3H, m), 7.75 (1H, d), 7.64 (1H, t) and 3.94 (3H, s).

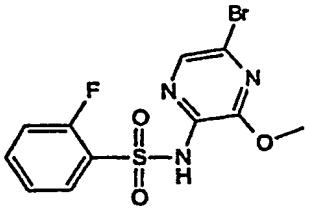
Example 13

N-(5-Bromo-3-methoxy-2-pyrazinyl)-2-ethenylbenzenesulphonamide



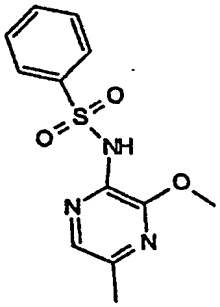
Example 14

N-(5-Bromo-3-methoxy-2-pyrazinyl)-2-fluorobenzenesulphonamide



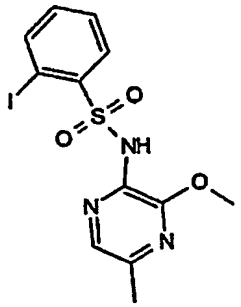
Example 15

N-(3-Methoxy-5-methyl-2-pyrazinyl)benzenesulphonamide



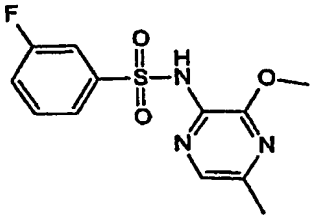
Example 16

N-(3-Methoxy-5-methyl-2-pyrazinyl)-2-iodobenzenesulphonamide



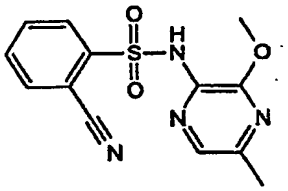
Example 17

N-(3-Methoxy-5-methyl-2-pyrazinyl)-3-fluorobenzenesulphonamide



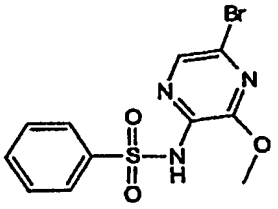
Example 18

2-[[(3-Methoxy-5-methyl-2-pyrazinyl)amino]sulphonyl]benzonitrile



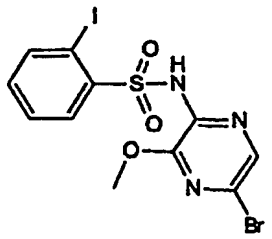
Example 19

N-(5-Bromo-3-methoxy-2-pyrazinyl)benzenesulphonamide



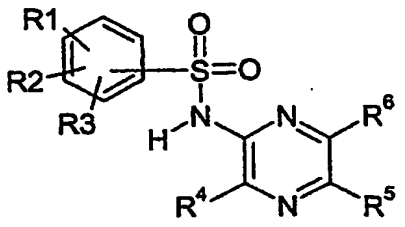
Example 19

N-(5-Bromo-3-methoxy-2-pyrazinyl)2-iodobenzenesulphonamide


I
O
S
H
N
O
N
O
N
Br

CLAIMS

1. A compound of formula (I) and pharmaceutically acceptable salts or solvates thereof for use in therapy:



(I)

in which
R^1, R^2 and R^3 are independently hydrogen, halogen or C_{1-6} alkyl;
R^4 is OR^9;
R^5 and R^6 are independently hydrogen, halogen, C_{1-6} alkoxy, C_{1-6} alkylthio, R^9, OR^9, NR^9R^{10} or SR^9;
R^9 and R^{10} are independently hydrogen, C_{1-6} alkyl, optionally substituted aryl, C_{1-6} alkyl-aryl or C_{1-6} alkyl-R^{11}; and
R^{11} is a 5- to 7-membered heteraromatic ring containing 1 to 3 heteroatoms selected from nitrogen, oxygen and sulphur.

2. A compound according to claim 1 in which one of R^1, R^2 and R^3 is methyl, ethenyl, cyano, chloro, fluoro, iodo or two are chloro or all three are fluoro.

3. A compound according to claim 1 or 2 in which R^4 is C_{1-6} alkoxy or C_{1-6} alkyl.

4. A compound according to any one of claims 1 to 3 in which R^5 and R^6 are hydrogen.

5. A compound according to claim 1 which is:

2,3-Dichloro-N-(3-methoxy-5-methyl-2-pyrazinyl)-benzenesulphonamide

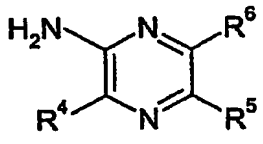
N-(6-Chloro-3-methoxy-2-pyrazinyl)-2,3,4-tifluorobenzenesulphonamide

3-Chloro-N-(6-Chloro-3-methoxy-2-pyrazinyl)-2-methylbenzenesulphonamide

2,3-Dichloro-N-(6-Chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide

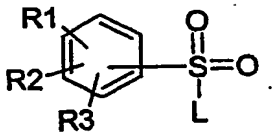
2,3-Dichloro-N-(5-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide
N-(5-Bromo-3-methoxy-2-pyrazinyl)-2,5-dichlorobenzenesulphonamide
N-(5-Bromo-3-methoxy-2-pyrazinyl)-3,5-dichlorobenzenesulphonamide
N-(5-Bromo-3-methoxy-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide
N-(5-Bromo-3-methoxy-2-pyrazinyl)-2,4-dichlorobenzenesulphonamide
N-(5-Bromo-3-methoxy-2-pyrazinyl)-3,4-dichlorobenzenesulphonamide
N-(5-Bromo-3-methoxy-2-pyrazinyl)-4-chlorobenzenesulphonamide
N-(5-Bromo-3-methoxy-2-pyrazinyl)-3-chlorobenzenesulphonamide
pyrazinamine and 3-chlorobenzenesulphonyl chloride.
N-(5-Bromo-3-methoxy-2-pyrazinyl)-2-ethenylbenzenesulphonamide
N-(5-Bromo-3-methoxy-2-pyrazinyl)-2-fluorobenzenesulphonamide
N-(3-Methoxy-5-methyl-2-pyrazinyl)benzenesulphonamide
N-(3-Methoxy-5-methyl-2-pyrazinyl)-2-iodobenzenesulphonamide
N-(3-Methoxy-5-methyl-2-pyrazinyl)-3-fluorobenzenesulphonamide
2-[[(3-Methoxy-5-methyl-2-pyrazinyl)amino]sulphonyl]benzonitrile
N-(5-Bromo-3-methoxy-2-pyrazinyl)benzenesulphonamide
N-(5-Bromo-3-methoxy-2-pyrazinyl)2-iodobenzenesulphonamide
and pharmaceutically acceptable salts and solvates thereof.

6. A process for the preparation of a compound of formula (I) which comprises reaction of a compound of formula (II):



(II)

where R^4, R^5 and R^6 are as defined in formula (I) or are protected derivatives thereof with a compound of formula (III):



(III)

where R^1, R^2 and R^3 are as defined in formula (I) or are protected derivatives thereof and L is a leaving group,
and optionally thereafter

- removing any protecting groups,
- forming a pharmaceutically acceptable salt.

7. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

8. A process for the preparation of a pharmaceutical composition as claimed in claim 2 which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1 with a pharmaceutically acceptable adjuvant, diluent or carrier.

9. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1 in the manufacture of a medicament for use in therapy.

10. A method of treating a chemokine mediated disease wherein the chemokine binds to one or more chemokine receptors, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1.

11. A method according to claim 10 in which the chemokine receptor belongs to the CCR chemokine receptor subfamily.

12. A method according to claim 10 or 11 in which the chemokine receptor is the CCR4 receptor.

13 A method of treating an inflammatory disease in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1.

14. A method according to claim 13, wherein the disease is asthma.

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ABSTRACT

The invention provides thienylsulphonamides for use in therapy.

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